REMARKS

By the foregoing amendments, claims 2-5, 9-20, 31-32, 37, 43 and 45 have been cancelled, and claims 1, 7, 26, 33, 38, 40 and 42 have been amended. Claims 1, 6-8, 21-30, 33-42 and 44 are pending in the case.

The Rejection under 35 USC 112, Second Paragraph

Claims 1, 6-8, 21-30, 33-42 and 44 stand rejected under Section 112, second paragraph, for indefiniteness. The Examiner points out that the claims should be amended to recite the elected invention. By the foregoing amendments, the withdrawn claims have been cancelled. Additionally, the elected claims have been amended to narrow their scope to always include IdIs. In some claims, e.g., claims 1 and 7, it was necessary to continue to refer to IPSCs and IPCs in order for the claim to make sense. If the amendments are not what the Examiner had in mind, he is invited to explain in more detail how the claims should be amended.

Claims 1 and 7-8 are rejected because critical elements of the claims are allegedly not defined. The Examiner argues that step (a) culture conditions are essential to the invention and should therefore be recited. Solely in the interest of expediting prosecution, Applicants have amended step (a) of claims 1 and 7 to reflect culture conditions that are favorable to the survival of IPSCs and ductal epithelial cells and substantially lethal to differentiated cells. Support for these amendments can be found in the specification at page 8, lines 19-23; page 15, lines 19-29; page 22, lines 12-16; and page 25, lines 16-17. It is believed that this amendment adequately addresses the Examiner's concerns.

Claim 37 is allegedly indefinite because there is no "marker" recited in claim 36. The structure of the antibody and its antigen is allegedly unclear. Solely in the interest of expediting prosecution, claim 37 has been cancelled.

Claims 38-39 are rejected as indefinite for failing to recite essential steps. Applicants respectfully submit that the term "serial transfer" is a term well known in the art. Further, the specification has several passages describing serial transfers. On page 17, lines 16-23, the specification states that serial transfer of ductal epithelium plus islet

foci (aggregates of IPSCs and IPCs where IdI growth has been initiated) to new culture flasks has been found to be useful in propagating and expanding IdI-producing cultures. In the alternative, only IdIs or IPSCs are serially transferred. The generated IdIs are useful in reversing the metabolic problems of insulin dependent diabetes (IDD). On page 25, lines 29-30, the specification states that the process described on the same page at lines 14-28 can be repeated several times by serially transferring ductal epithelium (or IPSCs) plus early-stage, proliferating IdIs in culture. In Example 5, the specification describes long term propagation of the IPSCs via serial transfers of small numbers of the ductal epithelium plus a few early-stage, proliferating IdIs to new culture flasks. Serial transferred cultures produced new IdIs far sooner than primary cultures and in higher numbers. Eventually, a point may be reached where serial propagation is no longer possible.

In view of the general description and exemplification of the serial transfer process, it is respectfully submitted that claims 38-39 are not indefinite. Withdrawal of the subject rejection is requested.

Claim 42 is allegedly indefinite because it is not clear whether the claim is directed to a body containing the implant or the isolated modified implant. By the foregoing amendment, claim 42 has been amended to recite "consisting essentially of" transitional language. It is believed that this amendment indicates that the claims is directed to the pancreas-like structure itself, whether it is located *in vivo* or if it has been removed possibly for transfer to another recipient.

In view of the foregoing amendments and remarks, it is respectfully requested that the Section 112, second paragraph rejections be withdrawn.

The Rejection under 35 USC 102(b)

Claims 6-8 stand rejected under Section 102(b) as anticipated by Langley, U.S. 5,447,863. The Examiner argues that the '863 reference inherently describes products that are identical to the claimed subject matter.

Although Applicants do not acquiesce in the Examiner's rejection, they have, in order to expedite prosecution, amended claim 7 to contain the same limitations as claim

6, i.e., that the β cells are at the center of the IdI and are 20-25% of the total cells of the IdI, the α or PP cells are in the outer cortex, and proliferating and undifferentiated cells are located in the inner cortex of the IdI. Applicants respectfully direct the Examiner's attention to page 13, lines 23-26 of the specification, wherein it is stated that as compared to *ex vivo* islets, such as those described by Langley, the claimed IdIs have 20-25% β cells, while *ex vivo* islets contain about 60% β cells. Applicants therefore respectfully submit that the claimed IdIs with 20-25% β cells are not disclosed expressly or inherently in Langley. Withdrawal of the subject rejection is respectfully requested.

The Rejection under 35 USC 112, First Paragraph

Claims 21-30, 40-41 and 42-44 stand rejected under Section 112, first paragraph as failing to comply with the written description requirement. The Examiner argues that there is no working example of treating diabetes with IdIs. On page 7 of the Office Action, the Examiner discusses *In re Fisher*, 166 USPQ (CCPA 1970) and the standard for enablement. It is therefore believed that the subject rejection also involves a non-enablement rejection.

Claim 21 is directed to a method of treating pancreatic disease by implanting the IdI of claims 6 or 7 into the tissue of a mammal. Claim 26 is directed to a method of treating pancreatic disease by culturing pancreatic cells to produce IPCs and IdIs, and implanting IPSCs, ductal epithelium, IPCs and/or IdIs into a mammal to produce a pancreas-like structure. Claim 40 is to a method of inducing neovascularization in a pancreatic implant in a mammal by implanting IPSCs, IPCs and/or IdIs. Claim 42 is directed to a pancreas-like structure produced by implantation of IPSCs, IPCs and/or IdIs.

The specification describes generally the treatment of diabetes by implantation of IdIs and other related cells or tissues into a patient, whereby the need for insulin therapy is reduced. See, e.g., page 9, lines 7-14; page 17, lines 21-30; page 18, line 21 to page 19, line 4; page 22, line 26 to page 23, line 22.

Applicants also respectfully direct the Examiner's attention to Example 3 which describes implantation of *in vitro* generated IdIs and ductal epithelium (grown in NOD mice according to methods described in the application), into the cortex of the kidney

capsule of syngeneic diabetic NOD mice. Controls were NOD mice that did not receive a transplant. After weaning from insulin, control NOD mice showed a rapid onset of overt disease. Implanted NOD mice maintained a near normal blood glucose level. Similar results were seen with intra-splenic implants. This indicates that the implanted ductal epithelium and IdIs are sufficient to provide the necessary insulin to maintain stable blood glucose over the course of the experiment.

The Examiner's attention is also directed to Example 12, wherein the implantation of encapsulated IdIs and ductal epithelium in the subcutaneous pocket on the shoulder of 2 diabetic mice is described. A third mouse received the implantation without the encapsulant (hyaluronic acid, HA). While one of the HA-implanted mice died of hypoglycemia (possibly due to overproduction of insulin by the implant), the other 2 mice saw a reversal of diabetes symptoms with no evidence of autoimmune graft destruction for 3 months.

Additionally, Example 16 describes the induction of angiogenesis by implanted IdIs. Two NOD-SCID mice received IdIs that were implanted into a dorsal skin-fold chamber. One week later, vascularization was observed to be greatly enhanced. Islet mass was also increased.

The Examiner's attention is further directed to Example 19, wherein intraperitoneal implantation of mouse IdIs and possibly IPSCs and IPCs is described. Figure 17 illustrates that injection of 300 clusters (IdIs) into the peritoneal cavity resulted in reduced blood glucose levels. Implantation of a greater number of IdIs (1,000) resulted in further reduction of blood glucose levels.

Based on the foregoing description and experiments involving implantation of IdIs, IPSCs, IPCs and ductal epithelium, it is respectfully submitted that Applicants have provided ample written description and enablement for treatment of diabetes. Applicants respectfully point out that the Examiner is obliged to accept the Applicant's teachings and experimental data, unless he has some evidence to contradict the Applicant's evidence (*In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971)). The Examiner has cited no reference or scientific reasoning that undermines or contradicts the Applicant's evidence. Applicants therefore respectfully submit that the subject application has fulfilled the

written description and enablement requirements, and withdrawal of the subject rejection is requested.

Closing Remarks

It is believed that the foregoing amendments and remarks bring the subject application into condition for allowance and notification of same is respectfully requested. If the Examiner believes a phone conference would expedite prosecution, he is invited to phone the undersigned at 303-268-0066.

Submitted herewith is a Petition for Extension of Time for 3 months and a check for $510.00 (small entity). No other fees are believed to be due with this submission. If this is in error, please charge any necessary fees to Deposit Account No. 19-5117.

Respectfully submitted,

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July 10, 2006
Date

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